

Signal focusing through active transport

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In biological cells and novel diagnostic devices biochemical receptors need to be sensitive to extremely small concentration changes of signaling molecules. The accuracy of such molecular signaling is ultimately limited by the counting noise imposed by the thermal diffusion of molecules. Many macromolecules and organelles transiently bind to molecular motors and are then actively transported. We here show that a random albeit directed delivery of signaling molecules to within a typical diffusion distance to the receptor reduces the correlation time of the counting noise, effecting an improved sensing precision. The conditions for this *active focusing* are indeed compatible with observations in living cells. Our results are relevant for a better understanding of molecular cellular signaling and the design of novel diagnostic devices.

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Cellular signaling relaying external or internal biochemical cues typically involves low copy numbers of messenger molecules, inevitably effecting appreciable fluctuations in the count of molecular binding events at specific receptors [1–12]. A similar limitation by counting noise is encountered in modern microscopic diagnostic devices to which sensitivity is a key factor [13]. Modern microscopic techniques reveal molecular signaling events and underline their inherent stochasticity in living cells [14–17]. Nevertheless molecular signaling pathways in biological cells operate at remarkable precision [18, 19].

The first heuristic argument about noise limitation to biological concentration measurements is due to Berg and Purcell assuming biochemical receptors to count the number N of specific molecules in a volume equal to their linear dimension a [2]. N is then limited by Poissonian noise $\delta N \sim \langle N \rangle^{1/2}$. The time between two independent measurements is set by the time $\tau_D \sim a^2/D$ needed to clear the volume by diffusion, D being the molecular diffusivity. Averaging over a time τ_m thus allows to $N_m \sim \tau_m/\tau_D$ independent measurements, reducing the noise by the factor $N_m^{1/2}$. The relative accuracy to measure a background concentration $\langle c \rangle$ is thus $\overline{\delta c^2}/\langle c \rangle^2 \sim (Da\langle c \rangle\tau_m)^{-1}$ [2]. When the additional binding dynamics to the biochemical receptor is explicitly taken into account, this relative error becomes [1]

$$\frac{\overline{\delta c^2}}{\langle c \rangle^2} = \frac{2}{k_{\text{on}}\langle c \rangle(1 - \langle n \rangle)\tau_m} + \frac{1}{\pi Da\langle c \rangle\tau_m}. \quad (1)$$

The first contribution stems from the Markovian (un)binding to the receptor at detailed balance conditions with binding rate k_{on} and average receptor occupancy $\langle n \rangle$. The second term is the diffusional noise, up to the factor π identical to the result by Berg and Purcell [2]. The prefactor of the diffusive term in Eq. (1) was recently refined heuristically [11]. Inspired by the early ideas of Berg and Purcell a number of studies unraveled the crucial role of diffusional noise in biochemi-

cal signaling [4, 5, 7–10] along with additional features such as receptor cooperativity [3] and facilitated diffusion [12]. Various experiments suggest that cells indeed operate very close to the fundamental accuracy limit [1].

Here we extend the result (1) to the case when the signaling molecules are not only freely diffusing in the cell but actively transported along cellular filaments by motor proteins [20, 21] effecting intermittent ballistic excursions [22–25]. Such an additional active component occurs when extracellular signaling molecules are taken up by the cell via endocytosis: the molecules are engulfed into submicron lipid vesicle and then intermittently transported through the cell by motors [26]. A similar combination of free diffusion and active transport occurs when virus particles invade a living cell [27]. However, even free molecules such as messenger RNA may attach to motors [28], or proteins move in directed fashion due to cytoplasmic drag [29]. To incorporate the active component we employ the theory of random intermittent search for hidden targets [30] which was recently used to analyze reaction kinetics in active media [31]. We show that active transport enables both faster as well as more accurate sensing: an active noise floor exists, but it can be significantly lower than the purely diffusive counting noise (1). This *active focusing* reduces the noise correlation time and enables the receptor to detect relative changes in concentration with higher accuracy. Our results also have direct implications to the design of active components in microscopic synthetic diagnostic systems based on molecular signals [13].

Model. We consider a signaling particle (vesicle, virus, mRNA, or protein) in 3-dimensional cellular space, randomly switching between a passive diffusion phase p with diffusivity D and an active ballistic phase a with velocity $\mathbf{v}(\Omega)$ of constant magnitude $v = |\mathbf{v}|$ [32] in the direction of the solid angle Ω following a Markovian dynamics (Fig. 1). Assuming ideally disordered cytoskeletal filament orientations, the spatial direction of active

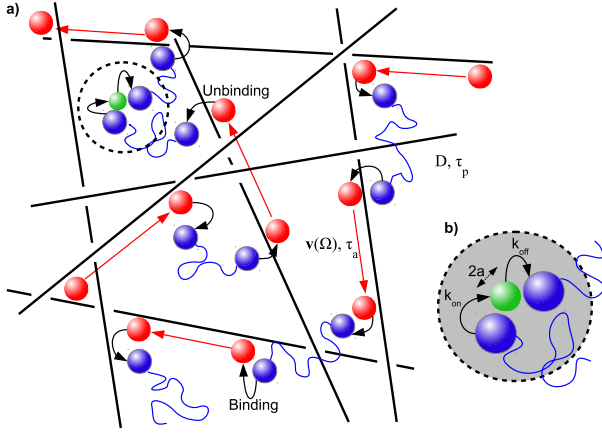


FIG. 1: Schematic of the model system: a) Each signaling particle performs passive thermal diffusion (blue phases) interrupted by active ballistic excursions with constant speed and random direction (red phases moving along the black motor tracks). The duration of both phases is distributed exponentially with mean times $\tau_{p,a}$. When the particle reaches the receptor (green sphere) it binds with on-rate k_{on} and dissociates with rate k_{off} . b) Magnification of the receptor region.

motion events is uniformly distributed. The duration of active/passive phases is exponentially distributed with mean $\tau_{a,p}$ [33]. The concentrations of freely diffusing and motor-bound signal particles are $c_p(\mathbf{r}, t)$ and $c_a(\mathbf{r}, \Omega, t)$. A receptor with radius a is placed at \mathbf{r}_0 . Then the fractional occupancy $n(t)$ of the receptor by a signal particle evolves according to a mean field kinetic scheme obeying detailed balance with on/off rates $k_{on/off}$,

$$dn(t)/dt = k_{on}c_p(\mathbf{r}_0, t)(1 - n(t)) - k_{off}n(t). \quad (2)$$

Assuming that the particle (un)binds to (from) the receptor only from (to) the passive mode [31], the coupled set of equations for the concentrations $c_{a,p}$ reads

$$\begin{aligned} \frac{\partial c_p(\mathbf{r}, t)}{\partial t} &= D\nabla^2 c_p + \int \frac{c_a}{\tau_a} d\Omega - \frac{c_p}{\tau_p} - \delta(\mathbf{r} - \mathbf{r}_0) \frac{dn(t)}{dt}, \\ \frac{\partial c_a(\mathbf{r}, \Omega, t)}{\partial t} &= -\nabla_{\mathbf{r}} \cdot (\mathbf{v}(\Omega)c_a) - \frac{c_a}{\tau_a} + \frac{c_p}{4\pi\tau_p}. \end{aligned} \quad (3)$$

The signaling typically occurs in two stages. In the initial phase a change in the concentration of the signaling particles occurs either by exchange with the extracellular space [19, 34] or by variation of the production and/or degradation rates. Upon re-equilibration (assumed to be much faster than the measurement time τ_m) the receptor reads out the concentration over the time τ_m in the *measurement phase*. In a diagnostic device equivalent phases will be observed after sample immersion and during detection periods. In an optimal signaling setup equilibration should be as fast as possible while the measurement phase should be as precise as possible. We now quantify the *speed* and *precision* of the two signaling phases.

Speed. We assume that the system equilibrates on a time scale over which the signaling molecules move a distance L of the order of the cell size (or that of a cellular compartment). At this stage we neglect the analyte-receptor binding dynamics and adopt a probabilistic view of Eqs. (3). The equilibration time τ_i is then defined by the mean squared displacement (MSD), $\langle |\mathbf{r}(\tau_i)|^2 \rangle = L^2$. The exact result is (see Supplementary Material, SM)

$$\begin{aligned} \langle |\mathbf{r}^2(t)| \rangle &= 2 \left\{ (v\tau_a)^2 e^{-\frac{t}{\tau_a}} - \frac{v^2 + 3D\tau_p^{-1}}{(\tau_a^{-1} + \tau_p^{-1})^2} e^{-\frac{t(\tau_a + \tau_p)}{\tau_a\tau_p}} \right. \\ &\quad \left. + \frac{\tau_p^{-1}(v\tau_a)^2 + 3D}{1 + \tau_a/\tau_p} t + \frac{3D\tau_p - (v\tau_a)^2(1 + 2\tau_p/\tau_a)}{(1 + \tau_p/\tau_a)^2} \right\}. \end{aligned} \quad (4)$$

Over a period of duration $\tau_a + \tau_p$, during which the directional persistence in the active phase causes a nonlinear time dependence of $\langle |\mathbf{r}^2(t)| \rangle$ and hence a local violation of the central limit theorem, an effective diffusive regime $\langle |\mathbf{r}^2(t)| \rangle \simeq t$ is established. Eq. (4) is a transcendental equation for τ_i , essentially depending on only three parameters: the typical distance covered in the active and passive phases, $x_a = v\tau_a$ and $x_p = \sqrt{D\tau_p}$, and the Péclet number $Pe = Lv/D$. To estimate the efficiency of active trafficking with respect to diffusion we compare τ_i with the purely passive equilibration time $\tau_0 \equiv L^2/(6D)$. The results for various Pe values (see Fig. 2e)) typical for biological systems are shown in Fig. 2a)-d).

Active transport is more efficient for larger particles (small D) in larger domains, a direct consequence of the finite motor velocity and instantaneous directionality of active motion. Namely, in terms of the MSD diffusion and active motion display different time scaling ($\simeq t$ versus $\simeq t^2$): considering only pure passive and active motion for $Pe < 6$ diffusion is more efficient. In the intermittent case the motion has a transient period of duration $\tau_a + \tau_p$, which corresponds to a parameter-dependent combination of both regimes during the relaxation towards the equilibrium partitioning between phases a and p . After this transient period an effective diffusive regime is established with diffusivity $D_{eff} = (D + x_a^2/(3\tau_p))/(1 + \tau_a/\tau_p)$, which may or may not be larger than D . τ_i can thus be smaller or larger than τ_0 . Trafficking of vesicles with $D \lesssim 10^{-2}\mu\text{m}^2/\text{s}$ therefore mostly profits from active motion, whereas active motion of smaller proteins with $D \sim 10\mu\text{m}^2/\text{s}$ will only be more efficient over large distances as in eukaryotic cells (especially for neurons), and only if accompanied by significant phases of passive diffusion. The observed features explain why it is profitable for a cell to use active transport for trafficking of larger particles [18, 35], despite demanding more cellular resources. Similarly, active diagnostics [13] can be faster and hence allow for a higher throughput.

Precision. Since the precision of the receptor measurement of the signal molecule concentration should be maximized we consider small deviations from the

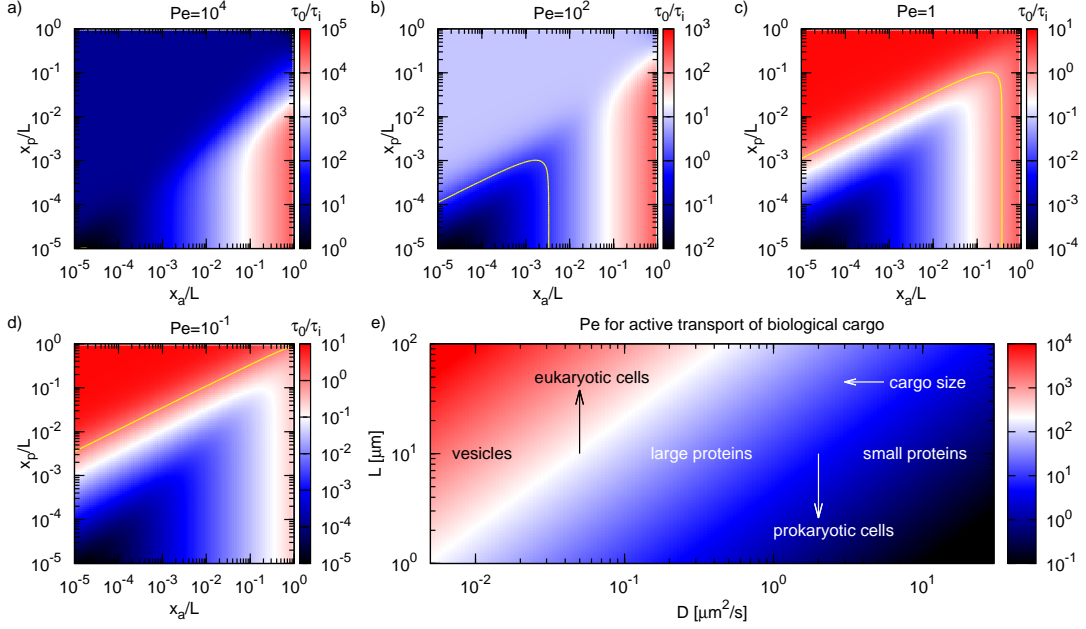


FIG. 2: a)-d) Equilibration times τ_0/τ_i for various Péclet numbers Pe from numerical inversion of Eq. (4). Yellow lines denote $\tau_0/\tau_i = 1$. When $\tau_0/\tau_i > 1$ active trafficking is more efficient. Note the different scales for τ_0/τ_i . e) Pe as function of cell (domain) size L and diffusivity D for biological cells [19, 34]. Arrows denote increasing particle size from right (small proteins) to left (large vesicles) and cell size from bottom (prokaryotic cells) to top (eukaryotic cells). The border between prokaryotic and eukaryotic cells is around $10\mu\text{m}$. For $Pe \sim 10^4$ (vesicles or large proteins in eukaryotic cells), active transport always improves the speed. For small proteins in eukaryotic cells and large proteins in prokaryotic cells ($10 \lesssim Pe \lesssim 10^2$), in addition to large x_a a large x_p is necessary for active transport to be more efficient. For $Pe \lesssim 10^{-1}$ active transport is always less efficient.

equilibrium values $n = \langle n \rangle + \delta n$ and $c_{p,a} = \langle c_{p,a} \rangle + \delta c_{p,a}$ [1], taking into account the detailed balance for the binding/unbinding transitions via $k_{\text{on}}\langle c_p \rangle/k_{\text{off}} = \exp(F/[k_B T])$, where F is the binding free energy [36]. Solving Eqs. (3) and following the ideas of Ref. [1] we use the fluctuation-dissipation theorem to obtain the power spectrum of the concentration fluctuations. Within the linear response regime and for receptor measurement times τ_m exceeding any correlation times, the relative error for the concentration measurement is [36]

$$\frac{\overline{\delta c_p^2}}{\langle c_p \rangle^2} = \frac{2}{k_{\text{on}}\langle c_p \rangle(1 - \langle n \rangle)\tau_m} + \frac{\Lambda(x_a, x_p)}{\pi D a \langle c_p \rangle \tau_m}. \quad (5)$$

Compared to Ref. [1] for passive diffusion our result (5) differs by the dimensionless factor $\Lambda(x_a, x_p)$ in the second term, for which always $\Lambda(x_a, x_p) \leq 1$ holds [36].

We now focus on the transport controlled regime in which $k_{\text{on}}\langle c_p \rangle, k_{\text{off}} \gg \tau_a^{-1}, \tau_p^{-1}$ and $k_{\text{on}}\langle c_p \rangle/k_{\text{off}} \gg 1$. Hence we neglect the first term in Eq. (5) and consider the remaining *active noise floor*. If the active excursions are short compared to the receptor size, $x_a/a \ll 1$,

$$\Lambda(x_a, x_p) \sim \frac{\sqrt{5} a x_p}{(\pi x_a)^2} \frac{\tanh^{-1} \left(\frac{(\pi x_a)^2}{\sqrt{5} a x_p} \left[1 + \frac{1}{3} (x_a/x_p)^2 \right]^{-\frac{1}{2}} \right)}{\left[1 + \frac{1}{3} (x_a/x_p)^2 \right]^{1/2}}. \quad (6)$$

In the biologically more important situation $x_a \gg a$,

$$\Lambda(x_a, x_p) \sim 1 - \tan^{-1}(\pi x_p/a)/(\pi x_p/a), \quad (7)$$

which has the lower bound $\Lambda_{\text{min}} \sim (\pi x_p/a)^2 [1 - (\pi x_p/a)^2]$ as $x_p/a \rightarrow 0$. This might suggest an approach towards an infinite absolute precision of the transport term as $x_p \rightarrow 0$. However, at fixed total concentration c_{tot} of signaling particles in the transport controlled regime we have that $\langle c_p \rangle = c_{\text{tot}}/(1 + \tau_a/\tau_p)$ corresponding to $\langle c_p \rangle \rightarrow 0$ as $x_p \rightarrow 0$, hence diverging relative fluctuations. Therefore, there still exists a noise floor to active sensing but it can be significantly reduced as explained below.

We gauge the sensing precision at equal c_{tot} and equal $\langle c_p \rangle$, corresponding to the lower and upper bounds for the gain of active focusing. For equal c_{tot} we compare the relative accuracy of measuring *different* concentrations of freely diffusing molecules in active and passive sensing, finding that the precision is always worse for active transport as compared to free diffusion (Fig. 3a-c) and asymptotic results in e) and f)) and becomes worse with longer active excursions. The reason is that despite reducing the absolute fluctuations by active dynamics we are measuring smaller and smaller effective concentrations. Conversely, Figs. 3d-f) shows that if we compare the precision at identical concentration $c_{\text{tot}}(1 + \tau_a/\tau_p)$ of free molecules the accuracy can be improved significantly

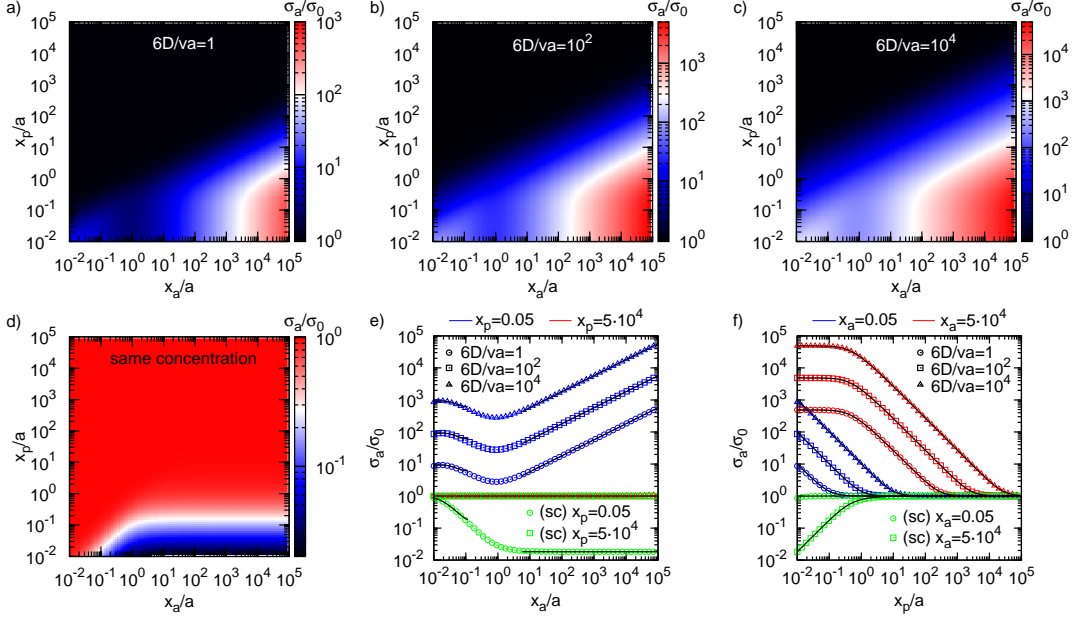


FIG. 3: a)-c) Fractional variance $\sigma_a = [\overline{\delta c_p^2}/\langle c_p \rangle^2]^{1/2}$ of concentration fluctuations at the receptor site for active trafficking compared to thermal diffusion, $\sigma_0 = [\pi D a c_{\text{tot}} \tau_m]^{-1/2}$ as function of the average distance traveled in both phases in units of the receptor radius a . In a)-c) the total concentration c_{tot} is kept constant, hence decreased sensing accuracy is solely due to exceedingly small equilibrium concentrations in the passive phase. d) σ_a/σ_0 for equal equilibrium concentrations (sc in parts e), f)) in the passive phase $\langle c_p \rangle$ for different total concentrations $= c_{\text{tot}}(1 + \tau_a/\tau_p)$: a strong increase in sensing accuracy is observed for $x_p/a \rightarrow 0$. a)-d) use the full results (5) and (S7) in SM [36]. e) Horizontal cross-sections of σ_a/σ_0 at large and small x_p (symbols) compared to the approximations (6), (7). f) Vertical cross-sections at large and small x_a (symbols) compared to the approximations (6), (7). Note the different scales for σ_a/σ_0 and the excellent agreement between full and approximate results. The non-monotonicity at small x_p is due to the interplay of signal focusing (smaller Λ) and decreasing $\langle c_p \rangle$.

as long as $x_p \lesssim a$ (otherwise, in this regime active trafficking does not affect sensing precision). The ingredients necessary to understand this reduced counting noise are: (i) only fluctuations on a scale $\sim a$ are relevant for the sensing accuracy and (ii) the receptor only 'sees' free particles. Hence, at finite temperatures perfect signaling corresponds to the situation in which upon release from the receptor the particles immediately bind to a motor and are swept away over distances $> a$. Concurrently diffusive displacements must be $\lesssim a$ to assure focused delivery in the sense that any unbinding from the motor only contributes if it occurs at $|\mathbf{r} - \mathbf{r}_0| \lesssim a$. This reduction of local concentration fluctuations by means of intermittent active excursions is exactly the *active signal focusing* mentioned above.

Conclusion. The last years have seen significant activity to explore the counting noise for purely diffusive scenarios [1–11] and to analyze the speedup of receptor binding due to the topological coupling of one- and three-dimensional diffusion for gene regulation in the facilitated diffusion model [12, 37]. In this Letter we fill the apparent gap in the quantitative assessment of the counting noise experienced by biochemical receptors measuring the local concentration of signaling molecules or com-

pounds in the case when an active transport component is present. This occurs for various signaling particles (proteins, mRNA molecules, vesicles containing signaling molecules, or viruses) by direct shuttling of these signaling cues by molecular motors or by cytoplasmic drag.

Compared to the purely diffusive signaling considered so far we showed that the counting noise (the limit to accurate receptor measurement) for active sensing can become significantly reduced due to active focusing. The only contributions to the counting noise stem from particles, which are actively transported to within the particle's typical free diffusion distance to the receptor. This reduces the correlation time of the receptor occupancy noise and renders the averaging over a measurement time τ_m more efficient. The importance of active signaling in cellular regulation is well recognized [38]. In agreement with our results, in biological systems active transport is indeed employed to move larger particles (e.g., vesicles or viruses) with intrinsically small D [19, 22–24, 27, 35]. As a result even during longer periods of detachment from motors these particles barely move [18, 22–24, 35]. The typical experimental values $x_a \simeq 0.5 - 10 \mu\text{m}$ [23–25, 35] for $a \simeq 1 - 10 \text{ nm}$ in fact fulfill the requirements of our model for signal focusing. However, as discussed here also

smaller particles such as mRNA and proteins experience active motion components [28, 29], effecting active focusing for their detection. In living cells the motor tracks are often not ideally disordered, as assumed here, but biased towards the receptor [38]. An expected net directional bias towards the receptor, while not impeding signal focusing as long as $x_a \gg a$ and $x_p \lesssim a$ [33], would enhance the rate of delivery and simultaneously increase the local concentration $\langle c_p(\mathbf{r}_0) \rangle$ at the receptor for equal c_{tot} . Signal focusing is thus inherent to active cellular signaling. Conversely, despite the great technological advance over the past years, molecular motor-powered diagnostic devices have not yet demonstrated a performance beyond the existing passive techniques, but a large superiority is much anticipated [13]. Our results confirm these expectations and present a first rigorous theoretical basis for their systematic improvement and development.

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Supplementary material Signal focusing through active transport

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In this Supplemental Material we summarise the calculations and full results for active transport coupled to reversible binding to a receptor.

SPEED

In this part we neglect the binding to the receptor (see main text for argumentation) and invoke a probabilistic interpretation of the model (i.e., concentrations \rightarrow probability densities). By Laplace transforming Eqs. (2) and (3) in the main text in time and Fourier transforming in space, $(\mathbf{r}, t) \rightarrow (\mathbf{k}, s)$ can be solved for \tilde{c}_a and \tilde{c}_p . The Laplace image of the mean squared displacement (MSD) for a particle starting at the origin in the passive phase is obtained from $\langle |\mathbf{r}^2(s)| \rangle = -\nabla_{\mathbf{k}}^2 (\int \tilde{c}_a d\Omega + \tilde{c}_p)|_{\mathbf{k}=0}$ and interchanging the order of differentiation with respect to \mathbf{k} and integration with respect to Ω :

$$\langle |\mathbf{r}^2(s)| \rangle = \frac{6D \left(1 + \frac{\tau_p^{-1}}{s + \tau_a^{-1}}\right) + 2\frac{\tau_p^2}{\tau_p} \frac{s + \tau_a^{-1} + \tau_p^{-1}}{(s + \tau_a^{-1})^3}}{s + \tau_p^{-1} - (\tau_a \tau_p)^{-1}/(s + \tau_a^{-1})}, \quad (\text{S1})$$

which can be inverted exactly to give Eq. (4) in the main text. The equilibration time τ_i is defined implicitly by $\langle |\mathbf{r}^2(\tau_i)| \rangle = L^2$, L being the linear dimension of the cell or its compartment. The transcendental equation for τ_i is solved numerically.

SENSING PRECISION

The Fourier transformed linearized Eqs. (1) read

$$\begin{aligned} -i\omega \delta \tilde{n}(\omega) &= -\tau_c^{-1} \delta \tilde{n}(\omega) + k_{\text{on}}(1 - \langle n \rangle) \delta \tilde{c}_p(\mathbf{r}_0, \omega) + k_{\text{off}} \langle n \rangle \beta \delta \tilde{F}(\omega) \\ -i\omega \delta \tilde{c}_a(\mathbf{k}, \Omega, \omega) &= -(i\mathbf{v}(\Omega) \cdot \mathbf{k} + \tau_a^{-1}) \delta \tilde{c}_a(\mathbf{k}, \Omega, \omega) + (4\pi\tau_p)^{-1} \delta \tilde{c}_p(\mathbf{k}, \omega) \\ -i\omega \delta \tilde{c}_p(\mathbf{k}, \omega) &= -(Dk^2 + \tau_p^{-1}) \delta \tilde{c}_p(\mathbf{k}, \omega) + \tau_a^{-1} \int \delta \tilde{c}_a(\mathbf{k}, \Omega, \omega) d\Omega + i\omega \delta \tilde{n}(\omega) e^{-i\mathbf{k} \cdot \mathbf{r}_0} \end{aligned}$$

where we have used the constraint imposed by detailed balance $\delta k_{\text{on}}/k_{\text{on}} - \delta k_{\text{off}}/k_{\text{off}} = \delta F/(k_B T)$ when linearizing the first of Eqs. (1) in the main text. Solving for $\delta \tilde{n}(\omega)$ we obtain

$$\delta \tilde{n}(\omega) = \frac{k_{\text{off}} \langle n \rangle \beta \delta \tilde{F}(\omega)}{\tau_c^{-1} - i\omega (1 + k_{\text{on}}[1 - \langle n \rangle](2\pi)^{-3} \int d\mathbf{k} \Xi(\mathbf{k}, \omega))}, \quad (\text{S2})$$

where $\beta = 1/(k_B T)$ and we have defined the correlation time $\tau_c \equiv (k_{\text{on}} \langle c_p \rangle - k_{\text{off}})^{-1}$ for two-state Markovian switching [1] as well as the two auxiliary functions defined as

$$\Xi(\mathbf{k}, \omega) \equiv -i\omega + Dk^2 + \tau_p^{-1} - (4\pi\tau_p\tau_a)^{-1} \Psi(\mathbf{k}, \omega) \quad (\text{S3})$$

$$\Psi(\mathbf{k}, \omega) \equiv \int_0^\pi d\theta \sin(\theta) \int_0^{2\pi} \frac{d\varphi}{\tau_p^{-1} - i(\omega - \mathbf{v}(\theta, \varphi) \cdot \mathbf{k})}. \quad (\text{S4})$$

We are interested in the low-frequency limit and hence take $\Psi(\mathbf{k}, \omega) \simeq \Psi(\mathbf{k}, 0)$. In this limit the integral over φ in $\Psi(\mathbf{k}, \omega)$ can be evaluated as a contour integral along the unit circle via the method of residues, while the second one is amenable directly leading to

$$\Psi(\mathbf{k}, 0) = \frac{4\pi}{vk} \tan^{-1}(v\tau_a k), \quad (\text{S5})$$

where $k \equiv |\mathbf{k}|$. Using Eq. (S5) we can obtain $\delta\tilde{n}(\omega)$ as a function of $\delta\tilde{F}(\omega)$ explicitly. The linear response function of the receptor occupancy (the coordinate) to a change in the free energy difference between bound and freely diffusing species (the thermodynamically conjugate force) is then $\delta\tilde{n}(\omega)/\delta\tilde{F}(\omega)$ and is related to the power spectrum of n via the fluctuation-dissipation theorem $S_n(\omega) = 2/(\beta\omega)\text{Im}[\delta\tilde{n}(\omega)/\delta\tilde{F}(\omega)]$. A change in concentration is equivalent to a change in F as a consequence to a change in chemical potential, $\delta c_p/\langle c_p \rangle = \beta\delta F$. Using this it can be shown [1] that $S_c(\omega) = (\beta\langle c_p \rangle)^2 |\delta\tilde{n}(\omega)/\delta\tilde{F}(\omega)|^{-2} S_n(\omega)$ leading to

$$S_c(\omega) = -\frac{2\langle c_p \rangle^2}{\omega k_B T} \text{Im} \left[\frac{\delta\tilde{F}(\omega)}{\delta\tilde{n}(\omega)} \right]. \quad (\text{S6})$$

We assume that the receptor measures and averages the concentration over a time τ_m much longer than any correlation time. We are thus interested in the low frequency limit $S_c(\omega \rightarrow 0)$ leading to $\overline{\delta c_p^2} = S_c(\omega \rightarrow 0)/\tau_m$ and hence take $\Xi(\mathbf{k}, \omega) \approx \Xi(\mathbf{k}, 0)$. Finally, cutting the integral in the inverse Fourier transform $|\mathbf{k}|_{max} = \pi/a$ to correct for a finite target size (and thereby avoid the UV divergence) we arrive at Eq. (5) in the main text with

$$\Lambda(x_a, x_p) = \int_0^1 \left(1 + \left(\frac{a}{\pi x_p q} \right)^2 \left[1 - \frac{\tan^{-1}(\pi x_a q/a)}{\pi x_a q/a} \right] \right)^{-1} dq. \quad (\text{S7})$$

The integral in Eq. (S7) can be evaluated exactly in the limits when the active excursions are either very short $x_a/a \ll 1$ or very long $x_a/a \gg 1$ compared to the size of the target and gives Eqs. (6) and (7) in the main text.

Now we have to evaluate the equilibrium concentration in the passive phase in the general case, where signaling is not necessarily transport controlled. In absence of a directional bias the concentration will be uniform in both the active and passive phase. Hence we only need to solve a system of linear equations for $\langle n \rangle$, $\langle c_p \rangle$ and $\int \langle c_a \rangle d\Omega$. It can be shown that the steady state concentration of freely diffusing molecules $\langle c_p \rangle$ is given by

$$\langle c_p \rangle = \frac{c_{\text{tot}} - V^{-1}}{2(1 + \tau_a/\tau_p)} - \frac{k_{\text{off}}}{2k_{\text{on}}} + \left[\left(\frac{c_{\text{tot}} - V^{-1}}{2(1 + \tau_a/\tau_p)} - \frac{k_{\text{off}}}{2k_{\text{on}}} \right)^2 + \frac{c_{\text{tot}} k_{\text{off}}}{k_{\text{on}}(1 + \tau_a/\tau_p)} \right]^{1/2}, \quad (\text{S8})$$

where V is the volume of the cell or its domain. For $k_{\text{off}}/(k_{\text{on}}\langle c_p \rangle) \rightarrow 0$ we obtain $\langle c_p \rangle = c_{\text{tot}}/(1 + \tau_a/\tau_p)$, where for convenience we have absorbed the term $1/V$ in the total concentration $c_{\text{tot}} - V^{-1} \rightarrow c_{\text{tot}}$. Expressing the ratio τ_a/τ_p in terms of x_p and x_a , $\tau_a/\tau_p = \frac{D}{|\mathbf{v}|} \frac{x_a}{x_p^2}$ we observe that $\langle c_p \rangle$ and hence the relative accuracy along with x_a and x_p in fact depends on the factor $\frac{D}{|\mathbf{v}|}$ as well.

[1] W. Bialek and S. Setayeshgar, Proc. Natl. Acad. Sci. USA **102**, 10040 (2005).